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(21) International Application Number: PCT/GB92/00877 (22) International Filing Date: 15 May 1992 (15.05.92) (30) Priority data: 9110651.8 15 May 1991 (15.05.91) GB (71) Applicant (for all designated States except US): STIEFEL LABORATORIES, INC. [US/US]; 2801 Ponce de Leon Boulevard, Suite 850, Coral Gables, FL 33134-6988 (US). (72) Inventors; and (75) Inventors/Applicants (for US only) : WOOD, John, Martin [GB/DE]; SCHALLREUTER, Karin, Uta [DE/DE]; Feldbehnkehrre 16, D-2085 Quickborn (DE). (74) Agent: BURFORD, Anthony, Frederick; W.H. Beck, Greener & Co, 7 Stone Buildings, Lincoln's Inn, London WC2A 3SZ (GB).		(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), CS, DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GB (European patent), GR (European patent), HU, IT (European patent), JP, KR, LU (European patent), MC (European patent), NL (European patent), NO, PL, RO, RU, SE (European patent), US. Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: COMPOSITION AND METHOD OF ENHANCING SUN TANNING (57) Abstract Sun tanning, especially of fair skin, is enhanced by topical application of a pseudocatalase prior to exposure to sunlight or UVB light. The preferred pseudocatalases are transition metal co-ordination complexes, especially manganese (II) bicarbonate.		

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COMPOSITION AND METHOD OF
ENHANCING SUN TANNING

5 The present invention relates to the enhancement of sun tanning and has particular, but not exclusive, application to the sun tanning of fair skin (ie. Types I and II skins).

10 The extent of sun tanning following exposure to sunlight or other source of UV light depends upon the type of skin. Those with fair skin (ie. Types I and II) do not readily tan and are much more liable to sunburn than those with dark skin (ie. Types IV and V). Existing sunscreen
15 preparations protect against sunburn but do not enhance tanning compared with the unprotected skin.

 It has now surprisingly been found that tanning can be enhanced by topical application of manganese (II)
20 bicarbonate or other pseudocatalases.

 We have disclosed in a co-pending Patent Application of the same priority and filing dates and corresponding to UK Patent Application No. 9110652, that pseudocatalase can
25 be used topically to treat vitiligo.

 By pseudocatalase, we mean a plasma membrane permeable physiologically acceptable compound which catalyzes the dismutation of H_2O_2 in vivo in analogous manner to catalase.
30

 Exposure of the skin to UVB radiation generates superoxide anion radicals which is a preferred substrate for human tyrosinase (40 times better than oxygen) thereby promoting melanin formation. However, the superoxide anion
35 radicals are dismutated into dioxygen and peroxide ion

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causing an undesirable increase in hydroxyl ion concentration unless catalase or some other competing mechanism removes peroxide ion. Thus, the presence of a pseudocatalase is believed to allow sufficient UVB exposure for superoxide anion radical formation to promote pigmentation in catalase deficient areas without burning or other cell damage.

According to a first aspect of the present invention, there is provided the use of a pseudocatalase in the manufacture of a topical composition for the enhancement of tanning of skin, especially fair skin, on exposure to sunlight or UVB light.

In a second aspect, the invention provides a topical sunscreen composition comprising a pseudocatalase, a sunscreen agent and a physiologically acceptable topical vehicle therefor.

In a third aspect, the invention provides a pseudocatalase for use in the enhancement of tanning of skin, especially fair skin, on exposure to sunlight or UVB light.

In a fourth aspect, the invention provides a method of enhancing tanning of skin, especially fair skin, which comprises applying to the skin an effective amount of a pseudocatalase.

In a fifth aspect, the invention provides use of a pseudocatalase to enhance tanning of skin on exposure to sunlight or UVB light.

The pseudocatalase can be any physiologically acceptable compound which catalyzes the dismutation of

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hydrogen peroxide. Some compounds such as Mn(II) bicarbonate are already known to be pseudocatalases and others can be determined by simple screening tests.

5 The presently preferred pseudocatalases are transition metal co-ordination complexes in which the inductive effect of the electron acceptor ligand enhances the redox effect of the metal on hydrogen peroxide dismutation. Usually, the metal will be Cu(I), Fe(II) or, especially Mn(II) and
10 the ligand will be bicarbonate. It is especially preferred that the pseudocatalase is Mn(II) bicarbonate complex. Said complex readily can be prepared by contacting manganous chloride with excess bicarbonate in aqueous solution.

15

 The pseudocatalase is formulated in a topical vehicle for use. Conveniently, the vehicle comprises a hydrophilic cream to which an aqueous solution or suspension of the pseudocatalase is added to form a cream or lotion.
20 Alternatively, the vehicle can be a bath oil although any other compatible topical vehicle can be used to provide a topical composition.

 Usually, the composition will contain a sunscreen
25 agent and other components such as emollients, perfumes etc conventionally used in sunscreen preparations. In particular, the composition can contain calcium ions, suitably added as calcium chloride, usually in a concentration of 5 to 20 mmol. Subject to compatibility
30 with the pseudocatalase and superoxide anion, any conventional sunscreen agent, such as Parsol MCX, or other component can be used.

35 The invention is illustrated in the following non-limiting Examples.

Example 1

5 Manganous chloride (380 mg) was added to a solution of sodium bicarbonate (2.3 g) in purified water (3.0 ml) at ambient temperature. The mixture was allowed to stand until the evolution of gas had ceased. The resultant pinkish brown liquid was mixed with a hydrophilic cream (Neribase) to provide a white cream.

10 Neribase is a cream vehicle containing Macrogol stearate 2000; stearic alcohol; liquid paraffin; white soft paraffin; polyacrylic acid; sodium hydroxide; disodium EDTA (i.e. ethylenediaminetetraacetic acid disodium salt); methyl and propyl Paraben (i.e. 4-hydroxybenzoic acid
15 methyl and propyl esters); and water.

The cream was applied to test skin areas of healthy volunteers having skin type II or III and, after a period of 20, 45 or 60 minutes, the treated skin exposed to UVB
20 light for 10 to 20 seconds. The UVB source was a Saalman UV-Test machine and the doses were 0.06, 0.05, 0.04, 0.03, 0.02 mJ/cm² (10 seconds) and 0.18, 0.15, 0.12, 0.09, 0.06 mJ/cm² (30 seconds). The degree of erythema/tanning of the treated area and untreated area was determined by
25 observation after 24 and 72 hours post-irradiation.

The results are set forth in Table I below. The erythema increase is indicated on the scale +, ++ and +++ with ++ and +++ presenting a darker tan.

TABLE I

	Sex/ age	Skin type	T ₁ min	T ₂ sec	24 h treated/ control side	72 h treated/ control side
5						
	M/27	III	20	10	no difference	no difference
10	F/22	III	20	10	+++ / +	++ / +
	F/25	III	20	10	+++ / ++	++ / +
	F/23	III	20	10	+++ / ++	+++ / +
15	M/30	III	20	10	+++ / ++	++ / +
	M/23	III	20	10	++ / +++	no difference
20	M/24	III	20	10	+ / ++	no difference
	F/25	II	20	10	+++ / ++	++ / +
25	F/28	II	20	10	+++ / ++	++ / ++

+ - +++ : grade of erythema / tanning

30

T₁ = time between application and UVB irradiation

T₂ = time of UVB irradiation

35

Example 2

40

The test of Example 1 was repeated using creams to which calcium chloride had been added to provide 5 mmole or 10 mmole calcium ion content. The results are set forth in Tables II and III below.

TABLE II

5 (5 mmol Ca ²⁺)						
	Sex/ age	Skin type	T ₁ min	T ₂ sec	24 h treated/ control side	72 h treated/ control side
10	F/26	III	20	10	+++ / ++	++ / +
	M/52	III	20	10	+++ / ++	++ / +
15	F/21	III	20	10	++ / +++	+ / ++
	F/22	III	20	10	++ / +++	+ / ++
	M/27	III	40	10	+ / ++	+ / ++
20	F/25	III	20	30	+++ / ++	++ / ++
	F/27	III	20	30	no difference	+ / ++
25	F/28	III	60	30	++ / +++	+ / ++
	F/19	II	20	10	++ / +++	+ / +++
30	M/32	II	20	10	+ / ++	+ / ++
	F/43	II	45	10	+++ / ++	+++ / ++
35	M/21	II	45	10	++ / +	++ / +
	M/27	II	60	10	no difference	no difference
	M/30	II	20	30	+++ / ++	+++ / ++
40	M/33	II	20	30	+++ / ++	++ / +

45 + - +++ : grade of erythema / tanning

T₁ = time between application and UVB irradiation
T₂ = time of UVB irradiation

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TABLE III

(10 mmol Ca²⁺)

	Sex/ age	Skin type	T ₁ min	T ₂ sec	24 h treated/ control side	72 h treated/ control side
5						
10	F/27	III	20	10	+ / ++	+ / ++
	M/50	III	20	10	+++ / ++	++ / +
	F/21	III	20	10	+++ / ++	+ + / +
15	F/22	III	20	10	no difference	no difference
	F/23	II	20	10	no difference	no difference
20	F/49	II	20	10	+ / ++	no difference
	M/25	II	20	10	++ / +	+++ / ++
25	F/47	II	45	10	+++ / ++	+++ / ++
	M/24	II	45	10	++ / +	++ / +
30	M/25	II	45	10	++ / +++	+ / ++

+ - +++ : grade of erythema / tanning

35 T₁ = time between application and UVB irradiation
 T₂ = time of UVB irradiation

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CLAIMS

1. A topical composition comprising a pseudocatalase, a
5 sunscreen agent and a physiologically acceptable topical
vehicle therefor.
2. A composition as claimed in Claim 1, which is free of
calcium ions.
- 10 3. A composition as claimed in Claim 1, which contains 5
to 20 mmol calcium ions.
4. A topical composition as claimed in Claim 1, wherein
15 the pseudocatalase is a transition metal co-ordination
complex.
5. A composition as claimed in Claim 4, wherein the
pseudocatalase is a Cu(I), Fe(II) or Mn(II) co-ordination
complex.
- 20 6. A composition as claimed in Claim 4, wherein the
ligand of said co-ordination complex is bicarbonate.
7. A composition as claimed in Claim 6, wherein the
25 pseudocatalase is a Mn(II)-bicarbonate complex.
8. A composition as claimed in Claim 7, wherein the
Mn(II)-bicarbonate complex has been obtained by contacting
manganous chloride with excess sodium bicarbonate in
30 aqueous solution.
9. A method of enhancing tanning of skin which comprises
applying to the skin an effective amount of a
pseudocatalase.

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10. A pseudocatalase for use in the enhancement of tanning of skin on exposure to sunlight or UVB light.

5 11. The use of a pseudocatalase in the manufacture of a topical composition for the enhancement of tanning skin on exposure to sunlight or UVB light.

12. Use of a pseudocatalase to enhance tanning of skin on exposure to sunlight or UVB light.

10

INTERNATIONAL SEARCH REPORT

International App. ion No

PCT/GB 92/00877

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)⁶

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.C1.5 A 61 K 7/42 A 61 K 7/48

II. FIELDS SEARCHED

Minimum Documentation Searched⁷

Classification System	Classification Symbols
Int.C1.5	A 61 K

**Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched⁸**

III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹

Category °	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	FR,A,2287899 (L'OREAL) 14 May 1976, see page 3, lines 3-11; page 9, lines 20-21; page 10, lines 1-13; claims ---	1-12
A	EP,A,0424033 (POLA CHEMICAL INDUSTRIES INC.) 24 April 1991, see the whole document ---	1-12
A	Patent Abstracts of Japan, vol. 14, no. 314 (C-737)[4257], 5 July 1990, & JP,A,2108612 (SHIZEN K.K.) 20 April 1990, see the abstract ---	1-12
A	US,A,4806344 (GASKIN) 21 February 1989, see the whole document ---	1-12
A	EP,A,0155344 (BLENDAX-WERKE R. SCHNEIDER GmbH & CO.) 25 September 1985, see example 5 ---	1-12
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⁹ Special categories of cited documents : ¹⁰

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed


"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
13-07-1992	30. 09. 92.
International Searching Authority	Signature of Authorized Officer
EUROPEAN PATENT OFFICE	

None Dagmar FRANK

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
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**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

GB 9200877
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This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 03/08/92
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